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EXAMINER
ZISKA, S

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1804
DATE MAILED: 03/05/96

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☑ This application has been examined ☑ Responsive to communication filed on 12/18/95 ☒ This action is made final.

A shortened statutory period for response to this action is set to expire three (3) month(s), zero (0) days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☑ Claims 1-31 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☑ Claims 1-31 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

PTOL-326 (Rev. 2/93)

This application should be reviewed for errors.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-31 are active and examined in this Office Action. The rejection of claims 1-31 under 35 U.S.C. 112, first paragraph, is maintained. Applicant's arguments, filed December 18, 1995, have been considered but not found to be persuasive. Applicants have argued the rejection as a utility rejection. However, the examiner did not make a utility rejection and therefore arguments pertaining to the utility rejection will not be addressed. The examiner did not require human clinical data; in fact, in citing the deficiencies of the specification such as lack of guidance, and lack of working examples, specific reasoning why the scope of the claims is not enabled, the examiner presented the basis for undue experimentation by one of skill in the art and tracked the language of the Forman factors, necessary for a 112 rejection.

Applicants have argued that the specification provides such guidance, citing particularly, for example, specification page 10, lines 24-35. However, contrary to applicant's arguments,the cited location merely discloses the amount to administer per kg of body weight and further discloses that the administration to humans is not directly proportional. Since the specification discloses that administration is not proportional but fails to further disclose how TO administer the DMDP for reasons set forth in the previous Office Action, the rejection is correctly made.

Applicants have argued that the examiner has allowed claim 13 and therefore has not questioned the credibility of the results. However, merely because the claim was not rejected under 112, does not mean the claim is free of the art. Further, the rejection was based on the limitation of the claims to mice and since claim 13 claims mice, that rejection is not applicable.

Applicants have argued that it is undisputed that SCID mice are accepted by those of skill in the art as reflective of the human immune system. However, this argument as made is incorrect since SCID mice per se do not have any human immune system components and therefore cannot possibly be reflective of any immune system other than their own. Applicants are presumably referring to SCID mice having transplanted human immune system components, in which case hu-SCID mice are old and well known in the art.

Regarding claims 10 and 11, applicants have argued that the specification need not disclose types and protocols of radiation or chemotherapy. However, the specification does not teach one of skill how to practice the invention as claimed for reasons set forth in the previous Office Action and the rejection is maintained. Applicants have continually requested that the examiner provide proof that one of skill in the art would doubt the truth or accuracy of the claimed invention and in doing so have continually argued a 101 utility rejection. The examiner has set forth in the previous Office Action the reasons using the Forman factors the reasons why undue experimentation would be required of one of skill to practice the invention as claimed. The examiner does not doubt the credibility of the invention as asserted by applicants and the rejection made was not made under 101.

Regarding claim 31, the phrase "in whole or in part" is vague and unclear and was the basis of a 35 U.S.C. 112, second paragraph, rejection, set forth in the previous Office Action. Secondly, contrary to applicant's further arguments, the claim does in fact recite ablation of stem cells in whole or in part and in view of the disagreement of the interpretation of the claim, it is suggested that the claim language be amended to more clearly claim that which applicant's intend. "Which part" may mean the bone marrow component, the liver component, the

peripheral component, or the spleen component. Further "which part" may mean any percentage from 1% to 99% and therefore the metes and bounds are indeterminate as previously stated in the prior Office Action. The examiner only gets one meaning out of the phrase and if the meaning is not the one intended by applicants, then amendment after consultation with the examiner is suggested in order to further the prosecution of the application.

The rejection of claims 1-23 and 31 under 35 U.S.C. 112, second paragraph, is maintained. Applicant's arguments have been considered but not found to be persuasive. Applicants have argued that the meaning of "in whole or in part" is clear. However, contrary to such arguments, the meaning is not clear nor clarified in the specification. Further, regarding the word "substantially", although terms in claims must be examined in light of the specification, the terms are not limited to the meaning in the specification and the word "substantially" does not automatically encompass only the range of the specification.

The rejection of claims 1-17 and 19-23 under 35 U.S.C. 103 as being unpatentable over Aldrovandi taken with Pinto is maintained. Applicants have argued from pages 10-21 that the examiner has not met the burden of presenting a prima facie case of obviousness; that the examiner has engaged in improper hindsight; that the prior art does not address the problem of rapid clearance. Regarding the last, no claim claims the limitation that DMDP causes rapid elimination of splenic macrophages and it is well known in the art that macrophages are involved in the immune response regarding the rejection of transplanted or injected tissues which the graft versus host rejection or host rejection of transplanted tissue. Pinto (Pinto, page 580, first column) discloses that DMDP decreases the number of endogenous macrophages and the results of a decreased number

of macrophages would be numerous in view of the major role of macrophages in maintaining the immune response.

Although applicants have argued that graft rejection and immunity to pathogens are disparate immune responses, macrophages play a role in both and one of ordinary skill, knowing that the level of endogenous macrophages has been decreased would expect to see altered responses in other macrophage-related functions. Therefore, applicant's arguments regarding the non-obviousness of the combination are not persuasive.

Applicants have argued the nonapplicability of the prior art of Aldrovandi and Pinto. However, contrary to such arguments, macrophages are known to be involved in maintaining humoral as well as cell mediated immunities and one of ordinary skill, knowing from Pinto that DMDP depletes macrophage levels, would expect to see the effects on all aspects of macrophage mediated functions, whether in tissue rejection or viral immunity. Note that if by reducing macrophage levels, one creates a type of immunosuppression, the immunosuppression of the entire animal system would prevent rejection of transplanted tissues. Applicants appear to be arguing that the art is directed to only pathogen-directed immunoincompetence. However, there is no teaching that different subsets of macrophages are engaged in different immune responses such as graft rejection or pathogen responses. One of skill, knowing that macrophages are involved in a variety of immune responses such as graft rejection or pathogen responses would have the reasonable expectation that a reduction in endogenous macrophage levels would reduce all other macrophage associated functions, lacking evidence to the contrary.

Applicants' arguments on page 16, stating that "treatment of HIV infection by depletion of endogenous macrophages is not the claimed invention" are not understood since claims 8 and 9 are directed to animals having an HIV infection. Macrophages are

known in the art to be viral reservoirs for HIV; depletion of macrophage obvious decreases the viral reservoir.

Applicants arguments regarding the teachings of Pinto regarding the use of immunomodulators are not persuasive since Pinto also discloses that DMDP eliminates macrophages in the spleen.

Applicants' arguments regarding endogenous leukocytosis are not persuasive. Pinto discloses rapid elimination of splenic macrophages and that leukocytosis occurred. One of skill, having transplanted non-autologous hematopoietic cells, would clearly benefit from the expansion of the transplanted cell population.

Applicants have argued with the motivation to combine the references as set forth by the examiner. However, abolition of the viral reservoir is but one motivation; the previous Office Action also set forth an additional motivation (page 6, top paragraph) addressing the expectation that one of skill would have had a reasonable expectation that autologous also expect a stimulation of the autologous lymphocytes in view of the leukocytosis effect seen by Pinto on the endogenous lymphocytes.

Applicants have argued that applicant's findings are novel regarding the knowledge of desirability of lowering the level of macrophages in order to prevent depletion of transplanted)non-autologous) hematopoietic cells. However, the role of macrophages in tissue rejection is old and well known in the art and has been addressed by the examiner on page 6, top paragraph, bottom paragraph to top paragraph on page 7, first paragraph on top of page 7.

Applicant's arguments regarding the problem of rapid clearance is not persuasive since tissue rejection is old and well known in the art.

The rejection of claim 18 under 35 U.S.C. 103 as being unpatentable over Aldrovandi and Pinto as applied to claims 1-17

and 19-23 above and further in view of Bernstein is maintained. Applicants have argued that Bernstein teaches that activation of macrophages appears to decrease HIV replication and that therefore such a teaching would hardly suggest to one skilled in the art that inactivation of macrophages in a host with HIV is desirable. however, contrary to such arguments, Bernstein discloses that LPS up regulates HIV expression by macrophage growth factors down regulate HIV expression. However, in view of Bernstein's disclosure that macrophage are latent HIV reservoirs, it would have been obvious to one of ordinary skill to deplete macrophages in order to reduce the viral reservoirs. Applicants have argued LPS stimulation and have not addressed the macrophage growth factor stimulation argument presented by the examiner. Applicants' further arguments regarding the teachings of Bernstein are not persuasive since only one aspect of the teachings of Bernstein have been argued.

The rejection of claims 24-30 under 35 U.S.C. 103 as being unpatentable over Berenson and Baum taken with Pinto is maintained. Applicants have misargued the teachings of Pinto and only argued one teaching, the teaching that administration of DMDP causes a decrease in antimicrobial resistance. However, Pinto also discloses that administration of DMDP also causes an immunosuppression and one of ordinary skill, knowing of the DMDP-induced immunosuppression would have expected the transplanted cells to engraft since the immune system was suppressed.

The rejection of claim 31 under 35 U.S.C. 103 as being unpatentable over Baum taken with Pinto is maintained. Applicants have argued only one teaching, the teaching that administration of DMDP causes a decrease in antimicrobial resistance. However, Pinto also discloses that administration of DMDP also causes an immunosuppression and one of ordinary skill, knowing of the DMDP-induced immunosuppression would have expected the transplanted

cells to engraft since the immune system was suppressed. Applicants have further argued that the observation of Pinto pertains to the endogenous system of a healthy animal. However, such arguments would be irrelevant since the transplanted cells would be transplanted into an immunosuppressed individual and less likely to be rejected whether the endogenous cells were active or not.

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

Papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the PTO FAX center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG (30 November 15, 1989). The CM1 Fax Center number is (703) 308-4227.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Suzanne Ziska, Ph.D., whose telephone number is (703)308-1217. In the event the examiner is not available, the examiner's supervisor, Ms. Jacqueline Stone, may be contacted at phone number (703) 308-3153.

SUZANNE E. ZISKA
PRIMARY EXAMINER
GROUP 1800